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Dialysis outcomes and analysis of practice patterns suggests the dialysis schedule affects day-of-week mortality

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The risk of death for hemodialysis patients is thought to be highest on the days following the longest interval without dialysis (usually Mondays and Tuesdays); however, existing results are inconclusive. To clarify this we analyzed Dialysis Outcomes and Practice Patterns Study (DOPPS) data of 22,163 hemodialysis patients from the United States, Europe, and Japan. Our study focused on the association between dialysis schedule and day of the week of all-cause, cardiovascular, and noncardiovascular mortality with day-of-week coded as a time-dependent covariate. The models were adjusted for dialysis schedule, age, country, DOPPS phase I or II, and other demographic and clinical covariates, and compared mortality on each day to the 7-day average. Patients on a Monday–Wednesday–Friday (MWF) schedule had elevated all-cause mortality on Mondays, and those on a Tuesday–Thursday–Saturday (TTS) schedule had increased risk of mortality on Tuesdays in all three regions. The association between day-of-week mortality and schedule was generally stronger for cardiovascular than noncardiovascular mortality, and was most pronounced in the United States. Unexpectedly, Japanese patients on a MWF schedule had a higher risk of noncardiovascular mortality on Fridays, and European patients on a TTS schedule experienced an elevated cardiovascular mortality on Saturdays. Thus, future studies are needed to evaluate the influence of practice patterns on schedule-specific mortality and factors that could modulate this effect.

Kidney International (2012) **81,** 1108–1115; doi:10.1038/ki.2011.481; published online 1 February 2012

KEYWORDS: day of week; DOPPS; hemodialysis; mortality; schedule

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Received 12 October 2010; revised 17 October 2011; accepted 22 November 2011; published online 1 February 2012

Hemodialysis (HD) patients usually experience relatively high mortality rates; for example, $\sim$23% per annum in the United States, 15% in Europe, and 9% in Japan. As the most common treatment of advanced kidney failure, HD typically requires patients to follow a strict treatment schedule, which typically entails receiving dialysis on a three times a week schedule, either Monday–Wednesday–Friday (MWF) or Tuesday–Thursday–Saturday (TTS). During the intervals between dialysis sessions, electrolytes, fluid, and various uremic toxins accumulate and, as a result, contribute to an increased risk of mortality. Therefore, the intermittent dialysis schedule, MWF or TTS, may put patients at a higher risk of death on certain days. In particular, patients on a MWF schedule may have higher risk of death on Mondays, whereas those on a TTS schedule may experience an elevated risk on Tuesdays, since these days follow the longest intervals without the benefit of dialysis.

Various studies have assessed the association between day-of-week-specific mortality risk and dialysis schedule. For example, Bleyer *et al.*[1] found a significantly higher risk of sudden death and cardiac-related death on Mondays for MWF schedule patients, and on Tuesdays for TTS schedule patients. Karnik *et al.*[2] identified modifiable risk factors for cardiac arrest in dialysis units, including age, diabetes, using a catheter for vascular access, and being hospitalized within the past 30 days. In addition, results from Karnik *et al.*[2] revealed that there is a higher risk of cardiac arrest on Mondays for MWF schedule patients. Bleyer *et al.*[3] applied a strict definition of sudden death and investigated the association between the timing of HD and occurrences of sudden death among HD patients. The authors found an increased risk of sudden death in the 12-h period after starting dialysis, and also in the 12-h period at the end of the weekend interval (that is, before starting HD, namely Monday and Tuesday).

For several reasons, previously published studies should be interpreted with caution. Most prior studies were based on relatively small sample sizes; most were confined to US patients, limiting their generalizability. Moreover, statistical analyses were lacking in several respects. For example, results were sometimes based on crude death rates without covariate adjustment. In addition, for the most part, these analyses did not examine interactions between weekday and patient characteristics. For example, it is possible that mortality elevations on given days may be accentuated for various patient subgroups; for example, older patients, diabetics, and patients with various comorbid conditions.

Our study uses data from the Dialysis Outcomes and Practice Patterns Study (DOPPS), an international prospective observational study of HD treatment and patient outcomes. The DOPPS-I (1996–2001) comprised over 17,000 patients in seven countries (France, Germany, Italy, Japan, Spain, United Kingdom, and the United States) from more than 300 dialysis facilities. The DOPPS-II (2002–2004) population included over 12,000 patients in 12 countries (DOPPS-I countries plus Australia/New Zealand, Belgium, Canada, and Sweden) from more than 300 dialysis facilities. The sampled facilities have at least 20–25 HD patients and represent all geographic regions and all types of facilities in each country. The DOPPS selects a random sample of HD patients within each participating facility. In this study, we carry out a comprehensive investigation of the association between day-of-week-specific death rates and dialysis schedule, in the United States, Japan, and several European countries (Belgium, France, Germany, Italy, Spain, Sweden, and United Kingdom). In addition to having a very large sample size and long follow-up period, the DOPPS database contains information on many demographic variables and comorbid conditions. As the end point is time to death, we used survival analysis (Cox regression) with day of the week serving as a time-dependent covariate. Cox regression is well-suited for this purpose as it is designed to handle a data structure where time until death is potentially censored and accurately tracks which patients are at risk on a particular weekday. Thus, Cox regression appropriately accounts for deaths and right censoring as they occur.

RESULTS

Baseline characteristics of the prevalent cross-section of patients are presented in Table 1 by region. Compared with US patients, European and Japanese patients were, on average, more likely to be men, have lower body mass index, and less likely to have diabetes and cardiovascular disease (CVD). European patients tended to be older than US patients, whereas Japanese patients were on average younger than US patients. Each of these differences was statistically significant ($P<0.05$). Subsequent models were constructed from both prevalent (cross-sectional) and incident patients.

In total, 4395 deaths were reported during the study period. Of the deaths, 2663 were among US patients, 1391 among European patients, and 341 among Japanese patients. In addition, 1744 out of 4395 (40%) deaths were caused by CVD. A total of 2489 out of 4395 (57%) deaths were among patients on a MWF schedule, whereas 1906 (43%) were among those on a TTS schedule.

The distribution of deaths by day of the week for each dialysis schedule group is shown in Figure 1. For MWF schedule patients, Monday had a much higher percentage of deaths for US, European, and Japanese patients (19.7%, 19.6%, and 17.9%, respectively). For TTS schedule patients, Tuesday had the highest percentage of deaths for US, European, and Japanese patients (19.2%, 16.9%, and 19.1%, respectively). The distributions varied a little by region. For MWF schedule patients, Friday appears to have the highest risk of death in Japan, with $\sim 1/5$ deaths occurring on that day. For TTS schedule patients, Monday

Table 1 | Demographics by region

	United States (*N*=4666)	Europe (*N*=5623)	Japan (*N*=3531)
Black (%)	35.8	1.5	0
Male (%)	54.2	57.8	61.8
Age (years)	61.1 (15.2)	62.1 (15.1)	59.7 (12.6)
BMI (kg/m^2)	25.1 (6.1)	23.9 (4.7)	20.3 (3.1)
Diabetes	48.5	23.3	26.9
CVD	74.9	65.8	46.3

Abbreviations: BMI, body mass index; CVD, cardiovascular disease.
Values in the parentheses are the standard deviations.
This table is based on prevalent cross-sections of hemodialysis (HD) patients participating in either Dialysis Outcomes and Practice Patterns Study (DOPPS) I or II. CVD corresponds to any of the following comorbid conditions: cerebrovascular disease, congestive heart failure, coronary heart disease, or other cardiovascular diseases.

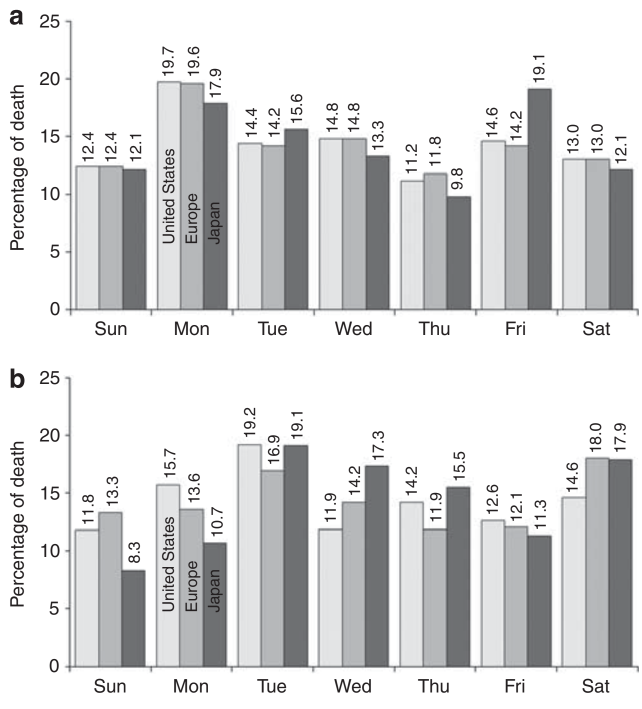

Figure 1 | Distribution of deaths by day of the week for patients receiving dialysis on Monday–Wednesday–Friday (MWF) and Tuesday–Thursday–Saturday (TTS). (**a**) For MWF schedule patients, Monday had a much higher percentage of deaths for the US and European patients. (**b**) For TTS schedule patients, Tuesday had the highest percentage of deaths for the US and Japanese patients.

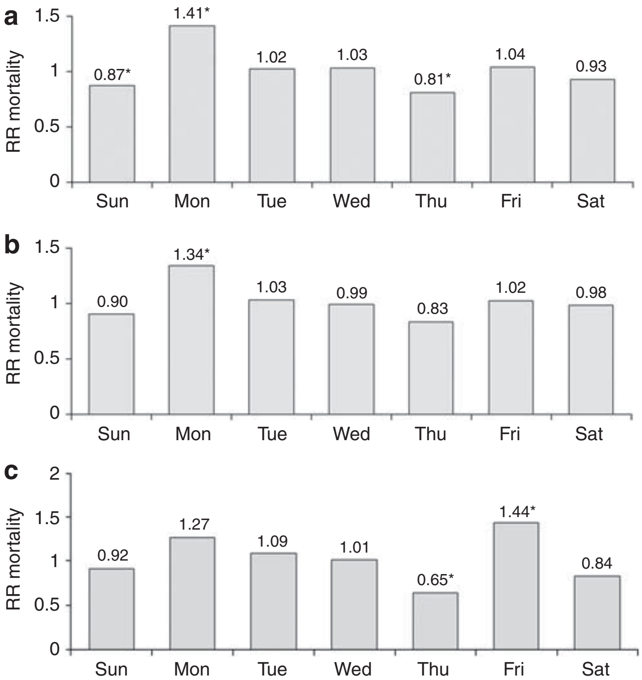

Figure 2 | Relative risk of mortality (all-cause) by day. (**a**) US patients receiving dialysis on Monday–Wednesday–Friday (MWF). Covariate-adjusted hazard ratios (HRs) of all-cause mortality by day of the week with MWF schedule for US patients. The reference is the average of 7 days of the week. The asterisks (*) mean that the effect is significant. (**b**) European patients receiving dialysis on MWF. Covariate-adjusted HRs of all-cause mortality by day of the week with MWF schedule for European patients. (**c**) Japanese patients receiving dialysis on MWF. Covariate-adjusted HRs of all-cause mortality by day of the week with MWF schedule for Japanese patients.

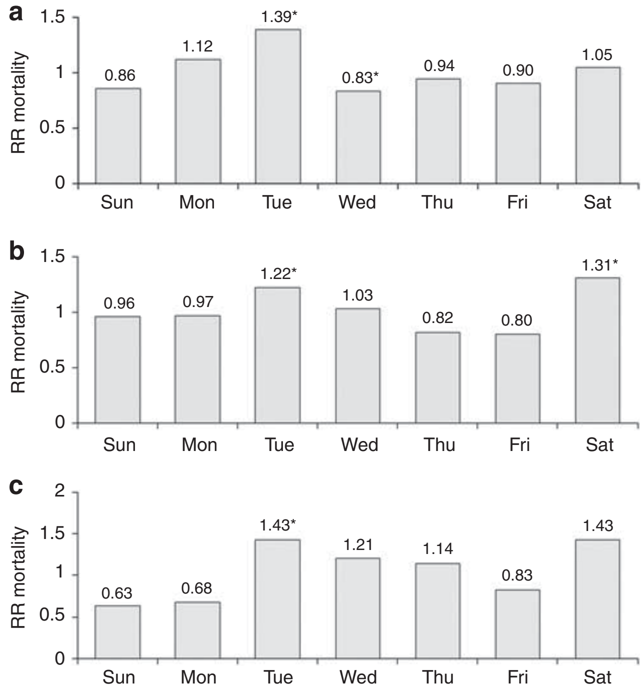

Figure 3 | Relative risk of mortality (all-cause) by day. (**a**) US patients receiving dialysis on Tuesday–Thursday–Saturday (TTS). Covariate-adjusted hazard ratios (HRs) of all-cause mortality by day of the week with TTS schedule for US patients. The reference is the average of 7 days of the week. The asterisks (*) mean that the effect is significant. (**b**) European patients receiving dialysis on TTS. Covariate-adjusted HRs of all-cause mortality by day of the week with TTS schedule for European patients. (**c**) Japanese patients receiving dialysis on TTS. Covariate-adjusted HRs of all-cause mortality by day of the week with TTS schedule for Japanese patients.

appears to have a higher risk of death in the United States (15.7%), whereas Saturday appears to have a higher risk of death in Europe and Japan (18% for both).

For each region, Cox regression models were used to estimate the covariate-adjusted day-of-week effect on death hazard, with day of the week coded as a time-dependent covariate. The model was set up so that the mortality hazard on each day was compared with the 7-day average. Figure 2 contains three sets of covariate-adjusted hazard ratios (HRs) for all-cause mortality by day of the week with MWF schedule for US patients (Figure 2a), European patients (Figure 2b), and Japanese patients (Figure 2c). Patients on a MWF dialysis schedule from the United States experienced a significant ($P<0.0001$) 41% higher risk of all-cause death on Mondays relative to the 7-day average. European patients experienced a significant 34% higher risk of all-cause death on Mondays versus the 7-day average ($P=0.001$), whereas patients from Japan experienced a 27% higher risk of all-cause death on Mondays ($P=0.154$), as well as a 44% higher mortality risk on Fridays ($P=0.04$).

Corresponding results for TTS schedule patients are shown in Figure 3, with each weekday again being compared with the overall average. A significant 39% higher risk of all-cause mortality was observed on Tuesdays for the US patients ($P<0.0001$). European patients experienced a significant 22% higher risk of all-cause death on Tuesdays ($P=0.043$) and a significant 31% higher risk of all-cause death on Saturdays ($P=0.013$). Japanese patients experienced a significant 43% higher risk of all-cause death on Tuesdays ($P=0.044$), as well as a 43% higher risk on Saturdays ($P=0.07$).

Figure 4 shows covariate-adjusted HRs of CVD and non-CVD mortality by day of the week for MWF schedule patients. In the United States, CVD mortality risk was higher by 45% on Mondays relative to the 7-day average ($P<0.0001$); the corresponding value for non-CVD mortality was 38% ($P<0.0001$). In Europe, patients experienced a significant 55% higher risk of CVD mortality on Mondays ($P=0.006$), while also experiencing a significant 27% higher risk of non-CVD mortality on Mondays ($P=0.023$). In Japan, CVD mortality risk was higher by 62% on Mondays ($P=0.098$); the corresponding value for non-CVD mortality was 10% ($P=0.674$). Japanese patients, however, experienced a significant 100% higher non-CVD mortality risk on Fridays versus the 7-day average ($P=0.001$).

In Figure 5, HRs of CVD and non-CVD mortality by day of the week for TTS schedule patients is displayed. In the

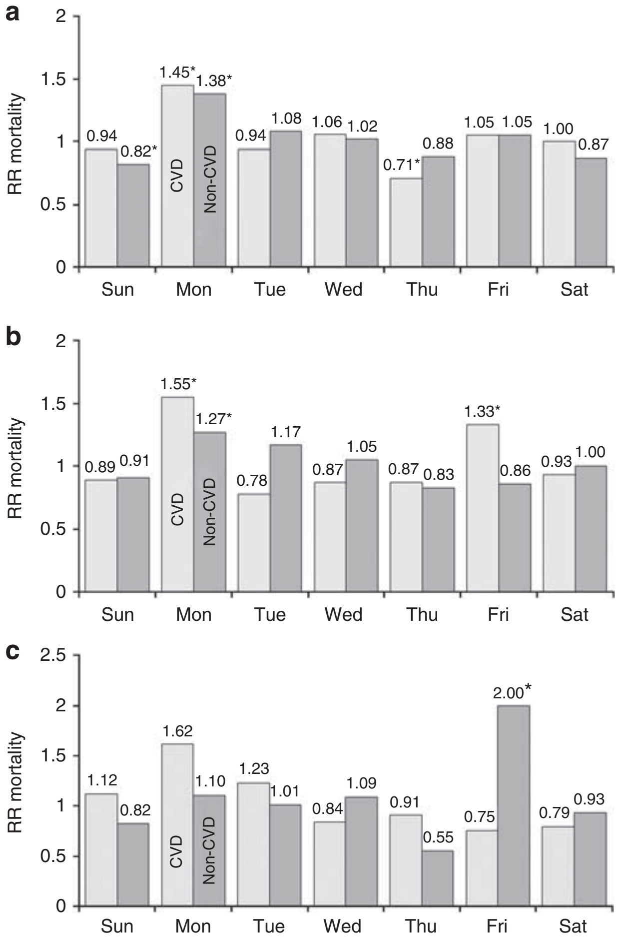

Figure 4 | Relative risk of mortality (cardiovascular disease (CVD) and non-CVD) by day. (**a**) US patients receiving dialysis on Monday–Wednesday–Friday (MWF). Covariate-adjusted hazard ratios (HRs) of CVD and non-CVD mortality by day of the week with MWF schedule for US patients. The reference is the average of 7 days of the week. The asterisks (*) mean that the effect is significant. (**b**) European patients receiving dialysis on MWF. Covariate-adjusted HRs of CVD and non-CVD mortality by day of week with MWF schedule for European patients. (**c**) Japanese patients receiving dialysis on MWF. Covariate-adjusted HRs of CVD and non-CVD mortality by day of the week with MWF schedule for Japanese patients.

United States, CVD mortality risk was higher by 56% on Tuesdays relative to the 7-day average ($P<0.0001$); patients also experienced a significant 26% higher non-CVD mortality risk on Tuesdays ($P=0.016$). In Europe, patients experienced a 43% higher risk of CVD mortality on Tuesdays ($P=0.058$), with the corresponding value for non-CVD mortality being 15% ($P=0.236$). However, European patients had an 88% higher risk of CVD death on Saturdays ($P=0.001$). In Japan, patients experienced a significant 75% higher risk of CVD mortality on Tuesdays ($P=0.037$) and also experienced a 93% higher CVD mortality risk on Saturdays ($P=0.034$). However, in Japan there was no evidence of higher non-CVD mortality on Tuesdays compared with the 7-day average (HR$=1.26$; $P=0.300$).

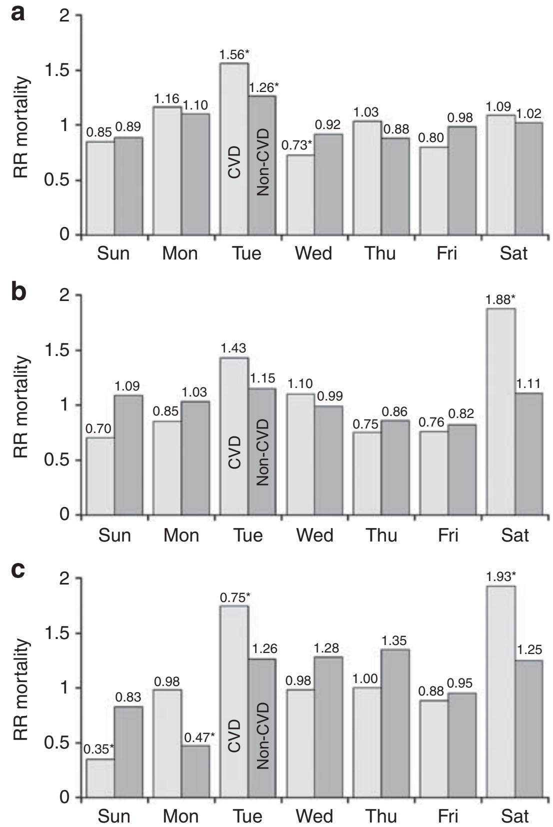

Figure 5 | Relative risk of mortality (cardiovascular disease (CVD) and non-CVD) by day. (**a**) US patients receiving dialysis on Tuesday–Thursday–Saturday (TTS). Hazard ratios (HRs) of CVD and non-CVD mortality by day of the week with TTS schedule for US patients. The reference is the average of 7 days of the week. The asterisks (*) mean that the effect is significant. (**b**) European patients receiving dialysis on TTS. HRs of CVD and non-CVD mortality by day of week with TTS schedule for European patients. (**c**) Japanese patients receiving dialysis on TTS. HRs of CVD and non-CVD mortality by day of the week with TTS schedule for Japanese patients.

Table 2 | RR of death (all-cause) by sex (United States, Europe, and Japan)

Comparison	Schedule	RR, male	RR, female	*P*-value (difference)
Monday vs. Avg	MWF	1.32	1.47	0.152
Tuesday vs. Avg	TTS	1.45	1.20	0.028

Abbreviations: Avg, average; MWF, Monday–Wednesday–Friday; RR, relative risk; TTS, Tuesday–Thursday–Saturday.

Cox models were fitted to all patients (that is, combining the United States, Europe, and Japan) to study which patient characteristics were associated with the day-of-week effect on all-cause mortality. For this part of the analysis, we focused specifically on the impact of sex, 14 comorbid conditions, and vascular access type on each of the two effects: the mortality elevation on Mondays (for MWF schedule patients) and that on Tuesdays (for TTS patients). The results are listed in Tables 2 and 3. None of the above-listed factors seemed to modulate the effects, with the possible exceptions of cancer

Table 3 | Modification of Monday and Tuesday effect by comorbid conditions and by using catheter as vascular access (United States, Europe, and Japan)

Comorbid conditions	Interaction with Monday and Tuesday	Comorbid conditions	Interaction with Monday and Tuesday
Cerebrovascular disease	1.03 (0.699)	HIV	0.79 (0.383)
Congestive heart failure	0.99 (0.891)	Hypertension	1.09 (0.210)
Coronary heart disease	1.05 (0.380)	Lung disease	1.00 (0.956)
Other cardiovascular diseases	1.02 (0.696)	Neurological disease	1.20 (0.039)
Cancer (other than skin)	0.84 (0.034)	Peripheral vascular disease	1.05 (0.400)
Diabetes	1.01 (0.924)	Psychiatric disorder	0.92 (0.166)
Gastrointestinal bleeding	1.01 (0.955)	Recurring cellulitis, gangrene	1.01 (0.899)
Catheter use	Interaction with Monday and Tuesday		
Catheter	0.98 (0.760)		

Numbers in the parentheses are the corresponding *P*-values.
A value of <1 (>1) means the factor was associated with a decreased (increased) risk of all-cause mortality on Mondays with Monday–Wednesday–Friday (MWF) schedule and on Tuesdays with Tuesday–Thursday–Saturday (TTS) schedule.

(other than skin) being associated with a lower risk of all-cause mortality on Mondays (for MWF schedule patients) and on Tuesdays (for TTS patients; HR = 1.18 for patients with cancer (other than skin), HR = 1.40 for patients without cancer (other than skin), *P*-value = 0.033); neurological disease being associated with a higher risk of all-cause mortality on Mondays (MWF schedule) and on Tuesdays (TTS schedule; HR = 1.59 for patients with neurological disease, HR = 1.33 for patients without neurological disease, *P*-value = 0.041); and sex, where the effect on Tuesday was higher for men on a TTS schedule.

A final Cox model was fitted, which combined DOPPS-I patients from the United States, Europe, and Japan, to determine whether time-dependent measures of blood pressure, potassium, sodium, ultrafiltration rate, intradialytic weight loss, residual renal function (RRF), and the use of diuretics modify the Monday and Tuesday effects. Table 4 shows that low ultrafiltration rate was associated with higher risk of all-cause mortality on Mondays with MWF schedule and on Tuesdays with TTS schedule. Diuretic use was associated with lower risk of all-cause mortality on Mondays with MWF schedule and on Tuesdays with TTS schedules.

DISCUSSION

Despite its proven value as a life-saving therapy, HD remains an intermittent intervention, most typically administered three times a week. Harmful waste products and fluid accumulated over the extended weekend interval may therefore put patients at a higher risk of death on certain days. Our results from the DOPPS in the US, European, and Japanese patients indicate that, in all three regions, HD patients have a higher risk of all-cause death on Mondays if they are on a MWF schedule, or Tuesdays if they are on a TTS schedule. Thus, findings from prior reports[1,3] are corroborated and expanded upon here. This day-of-week effect tends to be stronger for CVD than non-CVD death overall.

The European and Japanese data tend to confirm the effect, quite evident in the US data, of increased mortality on the day of the first dialysis session in the week. On the other hand, there are unique features to the results in Europe and Japan, such as high mortality on Saturdays in the TTS schedule, which may be due to practice patterns unique to those countries/regions. Such practice patterns could, for example, include continued aggressive/usual ultrafiltration and dialysis on Fridays or Saturdays (the last dialysis session of the week) in order to allow for the anticipated longer weekend gap in dialysis, despite the patients being closer to their target postdialysis weight at the time of the last dialysis session of the week. This could predispose to a greater degree of intradialytic hypotension and/or hypokalemia, which in turn would increase the tendency for CVD events, including sudden death. However, this mechanism, although plausible, remains speculative.

Nondialysis days had lower relative risks for mortality compared with dialysis days, perhaps because dialysis itself increases the risk of mortality. For HD patients, very large amounts of fluids and toxins are removed in a relatively short time period, particularly if the time elapsed since the last dialysis is long. This increases the potential for occurrence of intradialytic hypotension, which has previously been found to be a risk factor for mortality among HD patients.[4,5] Rapid reduction in postdialysis potassium may also be a contributory factor, as hypokalemia can enhance the risk for cardiac arrhythmia and sudden death, and this is more likely to occur on a dialysis day as opposed to the day preceding dialysis.

This study presents some evidence that the day-of-week effect is modulated by cancer (other than skin), neurological disease, sex, low ultrafiltration rate, and use of diuretics, but, apparently, not by other suspected factors including other comorbid conditions, blood pressure, serum potassium, serum sodium, intradialytic weight loss, and RRF (the hazard ratio for the interaction with day of the week in this instance was protective but statistically nonsignificant). Potential explanations toward the interpretation of some of these interactions are again speculative. For those with cancer, it could be speculated that the interaction with first day of the week was associated with lower mortality because the mechanism of death may predominantly be through noncardiovascular mechanisms. Those with neurological disease may have an accentuated early-in-the-week effect because of vascular diseases being the underlying cause for many types of neurological diseases (for example, cerebrovascular disease). Similarly, males have a greater association with

Table 4 | Modification of Monday and Tuesday effect by time-dependent factors (DOPPS-I: United States, Europe, and Japan)

Time-dependent covariate	Interaction with Monday and Tuesday	Time-dependent covariate	Interaction with Monday and Tuesday
Blood pressure low	0.84 (0.054)	Blood pressure high	1.19 (0.140)
Potassium low	0.85 (0.142)	Potassium high	1.15 (0.275)
Sodium low	1.08 (0.496)	Sodium high	1.06 (0.662)
Ultrafiltration rate low	1.28 (0.019)	Ultrafiltration rate high	0.94 (0.570)
Weight loss low	1.11 (0.292)	Weight loss high	1.07 (0.609)
RRF	0.80 (0.096)	Diuretic use	0.62 (0.003)

Abbreviations: DOPPS-I, Dialysis Outcomes and Practice Patterns Study, phase I; RRF, residual renal function.
Numbers in the parentheses are the corresponding *P*-values.
A value of <1 (>1) means the factor was associated with a decreased (increased) risk of all-cause mortality on Mondays with Monday–Wednesday–Friday (MWF) schedule and on Tuesdays with Tuesday–Thursday–Saturday (TTS) schedule.

CVD and hence may have an interaction with early-in-the-week mortality. Low ultrafiltration rate may at least in part reflect patients especially prone to dialysis-related hypotension, which is itself a predictor of worse patient outcomes, particularly the finding that modification of the early-in-the-week mortality risk in association with diuretic use has therapeutic implications, especially in patients with significant RRF who are likely to be responsive to diuretic therapy. This is consistent with previously published DOPPS findings showing a lower mortality among those receiving diuretics.[6] Low ultrafiltration may represent patients with low blood pressure to begin with, or those who are malnourished, thus being associated with higher early-in-the-week mortality. Clearly, associations found in these exploratory analyses require confirmation in future studies.

Some limitations of our study are as follows. Dialysis schedule was inferred from the date of reporting of dose of dialysis, which was collected once every 4 months. It was not possible to obtain the schedule information directly. In addition, the DOPPS data do not include the exact time of death or the timing of dialysis sessions, both of which would be useful additional data in further understanding the day-of-week effect. The secondary end point of CVD death is certainly of interest, but CVD death may not be ascertained completely or determined consistently across centers. Such limitations are typical of studies using large observational databases. Because of both the smaller sample size and lower event rate, inferences pertaining to Japanese HD patients are subject to substantially more uncertainty than those for US patients. Countries within Europe also have smaller sample sizes. However, these countries share similar genetic and environmental factors, as well as practice patterns, at least to some extent. In the analyses reported here, Europeans were considered as a single group, and conclusions were made about average effects over the 5–7 countries from this entire region. Larger samples from each country could examine differences within Europe. DOPPS-II also includes data from Canada, Australia, and New Zealand, but the sample sizes in these countries were too small to support reliable conclusions in this study. Noncompliance has been observed to be most common in the United States and least common in Japan. Non-adherence with dialysis sessions (‘shortening’ or ‘skipping’ sessions) has been associated with higher mortality as detailed in a previous DOPPS paper,[7] and would be expected to raise overall mortality rates. Unfortunately, there is insufficient information to assess the rate or effect of noncompliance in the DOPPS data. Finally, a substantial proportion (66%) of patients died in the hospital. Often, patients who are hospitalized would no longer follow their regular dialysis schedule. In this case, one would expect the observed day-of-week effect in this study to be somewhat attenuated. Further study that considered the potential confounding effect of hospitalization would be valuable.

Our results imply that there may be an advantage to a more frequent dialysis schedule in Europe, the United States, and potentially Japan. This is supported by the relatively low rates of mortality for patients receiving ‘daily dialysis’ based on various reports.[8–11] One could hypothesize that more frequent dialysis would reduce or eliminate the day-of-week effect and, therefore, lower mortality on HD. Many previous reports have found that daily dialysis is beneficial. For example, Woods *et al.*[8] found that for certain patients daily HD might have advantages over three times a week HD. Blagg *et al.*[9] observed that patients treated by short daily HD had a better survival rate than those treated by conventional HD. Kjellstrand *et al.*[10] reported that the survival of United States Renal Data System patients on short daily HD was 2–3 times lower than that of matched three times a week HD patients. Johansen *et al.*[11] examined survival and hospitalization between frequent HD patients and patients undergoing three times a week conventional HD. Their study found that there was a nonsignificant reduction in death risk for patients using short daily HD, whereas hospitalization patterns did not differ significantly between daily HD patients and their matched counterparts. There are many reasons why daily HD may improve patient survival. Daily HD can minimize fluid volumes,[10] and improve many abnormal physiological parameters and metabolic markers associated with a high mortality.[12–16] Quality of life has been reported to improve for patients on daily HD.[17,18] However, the term ‘daily’ has been defined differently in these studies. It can mean 5–6, 5–7, or 4–7 times of dialysis per week. Hence, there is the possibility that death rates are still elevated on the first and/or last day of dialysis. Therefore, our results do not imply directly that a more frequent dialysis could reduce mortality. We would need to analyze the data using a cohort that received daily dialysis in order to determine whether day-of-week effect really disappeared and, hence, whether mortality was reduced.

Bliwise *et al.*[19] investigated the association of HD treatment shift with continued survival among elderly patients. Their study found that the morning-shift HD patients survived significantly longer than the afternoon-shift patients. In the present study, we observed a higher risk of all-cause mortality among European patients on Saturdays on a TTS schedule and a higher risk of CVD mortality among European and Japanese patients on Saturdays on a TTS schedule.

In summary, we have carried out a comprehensive analysis of the interaction between dialysis schedule and day-of-the-week-specific mortality among HD patients in the United States, Europe, and Japan. Limitations associated with the DOPPS database suggest future directions for research in this area. In particular, future studies aimed at evaluating the benefit of additional weekly dialysis sessions or alternate-day dialysis should also assess the impact of schedule on day-of-week-specific mortality. Utilization of diuretics among those with significant RRF is another potential area fertile for further study, in addition to examination of other practice patterns that can reduce early-in-the-week mortality for those on conventional three times a week HD schedule, as this is likely to remain the norm for the vast majority of HD patients, at least for the foreseeable future. Further study of data with the exact time of death and the timing of dialysis sessions would be valuable in further understanding the day-of-week effect.

MATERIALS AND METHODS

Data were obtained on the US, Japanese, and European (Belgium, France, Germany, Italy, Spain, Sweden, and United Kingdom) patients from the DOPPS phases I and II. The overall design of the DOPPS has been described in some detail previously.[20,21] In total, the study population consisted of 22,163 patients: 9227 were from the United States, 8517 from Europe, and 4419 from Japan. For each patient, follow-up began at entry into the DOPPS. Patients were then observed until the earliest of death, transplant, loss to follow-up, or the end of the observation period: 31 December 2001 for phase I patients, and 31 December 2004 for Phase II patients. The mean follow-up time is 569 days for phase I patients and 564 days for phase II patients. Approximately 5% of patients received a transplant, and 4% of patients withdrew from the study. The primary outcome of interest is death (all-cause, CVD, and non-CVD). The date and cause of death were recorded. CVD mortality was defined as death with primary cause being any of the following: acute myocardial infarction, hyperkalemia, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary edema due to exogenous fluid, or congestive heart failure.

Baseline data on demographics, laboratory values, medical history, and medications were collected at the start of participation in the DOPPS. Thereafter, longitudinal data were collected at 4-month intervals, including updated hospitalization events, vascular access, laboratory values, medications, dialysis prescription, dialysis dose, and RRF. Detailed information is also reported for the final dialysis session in the 4-month period, including the date when dialysis was received. For purposes of analysis, if the reported date was a Monday, Wednesday, or Friday, the dialysis schedule was considered to be MWF in the corresponding 4-month interval. The TTS dialysis schedule was defined in a similar manner. If this date was missing or was a Sunday, the dialysis schedule was carried over from the preceding 4-month reporting interval. Approximately 79% of patients did not switch the dialysis schedule in this study, 13% patients switched once, either from MWF to TTS or from TTS to MWF, and 8% patients switched more than once.

Table 5 | Coding for time-dependent covariates

Time-dependent covariate	Sun	Mon	Tue	Wed	Thu	Fri	Sat
Z_1	−1	1	0	0	0	0	0
Z_2	−1	0	1	0	0	0	0
Z_3	−1	0	0	1	0	0	0
Z_4	−1	0	0	0	1	0	0
Z_5	−1	0	0	0	0	1	0
Z_6	−1	0	0	0	0	0	1

Baseline characteristics for prevalent patients (at the start of DOPPS I and II, $n = 13{,}820$) were summarized, with simple means for continuous variables and proportions for categorical variables.

The covariate of interest is the day of the week (Sunday, Monday, …, Saturday), which was coded as a time-dependent covariate in a Cox model, with time of origin as the first ever HD day. As patients were not under observation until they entered the DOPPS study, using timescale of days since study entry can be subject to left-truncation bias; therefore, we used days since onset of dialysis (dialysis vintage) as the timescale. Adjustment covariates included sex, race, 14 comorbid conditions (coronary heart disease, cancer other than skin, other CVD, cerebrovascular disease, congestive heart failure, diabetes, gastrointestinal bleeding, HIV/AIDS, hypertension, lung disease, neurological disease, psychiatric disorder, peripheral vascular disease, and recurrent cellulitis), body mass index (grouped as <20, 20–25, 25–30, and $\geqslant 30\,\text{kg/m}^2$), and vascular access (catheter use). Dialysis schedule, country, phase, and age group (18–29, 30–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and $\geqslant 70$ years) were adjusted through stratification. As patients from the same facility may be correlated because of shared practice patterns, valid statistical procedures must account for intracluster dependence, which was done using a robust ('sandwich') estimator of the covariance.[22]

Cox models were fitted to each region (United States, Europe, and Japan) separately. In all models, day of the week was coded such that each day was compared with the average of the 7 days of the week. Table 5 shows the coding of the time-dependent covariates related to day of the week. The average of the 7 days of the week is constrained to be zero in the model; therefore, each day was compared with this geometric average (that is, zero). The comparison of each level of a categorical predictor with the average is as defensible statistically as the comparison of each level with a reference level. The former is used much less frequently than the latter, but is the best choice for our analysis.

Further analyses used Cox models fitted to patients from all three regions combined, in order to study whether sex, 14 comorbid conditions, and vascular access (catheter use) modified the day-of-week effect. Models including interactions between region and day of the week have been compared with those without such interactions. As only small differences in estimates are observed between these two models, only results from the latter models are reported in this article. Moreover, in assessing the potential modifiers of the day-of-week effect, we found that the interactions between the modifiers and Mondays (for MWF schedule patients) are similar to those between the modifiers and Tuesdays (for TTS schedule patients); thus, in the models reported, these interactions are assumed to be equal and combined. Furthermore, another Cox model was fitted to the laboratory covariates of all patients (blood pressure, potassium, sodium, ultrafiltration rate, weight loss, RRF, and the use of diuretics). Each of these variables, except RRF and diuretic use, was categorized into three groups: low (lowest quartile), normal (middle two quartiles), and high (highest quartile). These time-dependent covariates were measured monthly in the unit, and weight loss was measured with each treatment. However, the DOPPS updated such measures only every 4 months. In this last time-dependent analysis, results were based on DOPPS-I data because only baseline potassium and sodium values were available in DOPPS-II.

In this study, the covariate of interest is day of the week (Sunday, Monday, …, Saturday). We defined time-dependent covariates based on the day of the week. Cox regression analyses used the PHREG procedure (SAS Institute, Cary, NC), and handled time-dependent covariates and left truncation through the counting process style of input. Facility clustering effects were accounted for through the robust sandwich covariance estimates. In the SAS PHREG procedure, this is implemented using the COVS(AGGREGATE) option, with ID specified as facility (SAS 9.2 documentation, example 64.11 in the PHREG procedure[23]). As implied, all statistical analyses were conducted using SAS V9.2 (SAS Institute).

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

Editorial assistance was provided by Ms Shauna Leighton, a Medical Editor at the Arbor Research Collaborative for Health, (Ann Arbor, MI). The DOPPS is administered by Arbor Research Collaborative for Health and is supported by scientific research grants from Amgen (since 1996), Kyowa Hakko Kirin (since 1999, in Japan), Genzyme (since 2009), and Abbott (since 2009), without restrictions on publications. The statistical methodology development and analysis for this investigation were supported in part by a National Institutes of Health grant (R01DK070869) to Professors Schaubel and Kalbfleisch.

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